REMARKS

Applicants thank the Examiner for total consideration given the present application. Claims 1-17 are pending in the present application. Claim 1 is independent. By this response, claims 1 and 4 are amended. Favorable reconsideration and allowance of the present application are respectfully requested in view of the following remarks.

Objections to the Claims

Claims 1 – 17 are objected to due to informalities. Specifically, claim 1 is objected to as having an extra period after EEG and as having unusual word spacing. Claim 4 is objected to as unclear with respect to which head surface is being referred to. Applicants hereby amend these claims to resolve the above-noted informalities. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

35 U.S.C. § 103 Rejection – Fox and Vilsmeier

Claims 1-5 and 7-17 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Fox et al. (USPN 2003/0050527 A1) (hereinafter "Fox") in view of Vilsmeier (USPN 7,194,295 B2) (hereinafter "Vilsmeier"). Insofar as it pertains to the presently pending claims, Applicants respectfully traverse this rejection.

Swearing Behind Vilsmeier

Applicants respectfully note that Vilsmeier has a U.S. filing date of April 26, 2002 and an Application publication date of October 2, 2003. The present Application has a foreign priority date of October 17, 2002. Applicants therefore respectfully submit that Vilsmeier can only be applied as a reference against the present invention under 35 U.S.C. §102(e). Applicants further submit that because Vilsmeier's foreign priority application, EP 02007218, filed on March 27, 2002, was a non-PCT application published in German, Vilsmeier's effective U.S. filing date is April 26, 2002 for the purposes of analysis under 35 U.S.C. §102(e).

Applicants hereby submit a declaration under 37 CFR §1.131 stating that the present invention was conceived prior to April 26, 2002. Applicants also hereby submit a certified translation of Finnish Application FI 20021858 to establish a priority filing date of October 17, 2002.

Summary

At least in view of the above, Applicants respectfully submit that without recourse to the Vilsmeier reference, the present rejection of claims 1 – 5 and 7 – 17 is incomplete and improper. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103 Rejection – Krause

Claim 6 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Fox in view of Vilsmeier in further view of Krause et al. (U.S. Patent 6,711,432). Insofar as it pertains to the presently pending claims, Applicants respectfully traverse this rejection.

Applicants respectfully submit that, having sworn behind Vilsmeier, the present rejection is incomplete and improper for at least the same reasons as set forth with respect to claims 1 – 5 and 7 – 17. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Naphtali Y. Matlis, Reg. No. 61,592, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: November 13, 2009

Respectfully submitted,

By ______________________

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Attachments

PATENT
0365-0625PUS1

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jarmo RUOHONEN

Application No.: 10/529,473 Confirmation No.: 8171

Filed: March 28, 2005 Art Unit: 3737

For: METHOD FOR THREE-DIMENSIONAL MODELING OF THE SKULL AND INTERNAL STRUCTURES THEREOF Examiner: J. Cwern

DECLARATION UNDER 37 C.F.R. § 1.131

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Jarmo Ruohonen, hereby declare that:

1. I am the Inventor of the invention disclosed and claimed in the United States Patent Application No 10/529,473

2. I am aware of the prosecution history of United States Patent Application No. 10/529,473, which was filed in the U.S. Patent and Trademark Office on March 28, 2005, based upon International Application PCT/FI2003/000772 filed in Finland on October 16, 2003, and that a claim of Priority of Application No. 20021858, filed in Finland on October 17, 2002 was claimed under 35 USC § 119 in United States Patent Application No. 10/529,473.

3. The subject matter of United States Patent Application No. 10/529,473 is included in Application No. 20021858, filed in Finland on October 17, 2002.

4. To my knowledge, and in view of the factual evidence supplied herewith, the present invention was conceived in Finland prior to April 26, 2002, which is the filing date of United States Patent 7,194,295 to Vilsmeier, cited by the Examiner in the Official Action dated May 13, 2009, in the above-identified application. This fact is evidenced by the attached Draft Patent Specification for FI 20021858 and English translation thereof. This is further evidence by the attached signed statement commemorating a meeting prior to April 26, 2002 where I presented the Draft Patent Specification to Nexstim, an assignee of the present Application, and an English translation thereof as well.

5. I declare that all the above identified acts were carried out in Finland, a WTO member country.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statement may jeopardize the validity of the application or any patent issuing thereon.

November 13, 2009
Date

Jarmo Ruohonen

MEETING XXXXXXXX 1.30 p.m.

SUBJECT: Standard head

Karhu and Ruohonen presented the idea of using an MRI standard head in TMS/MEG/EEG examinations. In the method, a positioning device is used to define the outer surface of the head of a person and to deform the MRI images of a second person in such a way that the outer shapes correspond to each other.

The method is advantageous in the planning, analysis, and visualization of TMS/MEG/EEG measurements. In particular, the visualization tools can also be used when MRI images of some test subject/patient are not available.

Those present received a confidential written 8-page description of the method in the form of a patent application dated XXXXXXXX.

Antti Ahonen, 4D Neuroimaging

Jari Karhu, Nexstim

Jarmo Ruohonen, Nexstim

PATENT APPLICATION

FORMING THE SHAPE OF MAGNETIC IMAGES OF THE HEAD IN MAGNETIC STIMULATION OF THE BRAIN AND IN ELECTRO AND MAGNETOENCEPHALOGRAPHY

INVENTOR

JARMO RUOHONEN

APPLICANT

NEXSTIM OY

FORMING THE SHAPE OF MAGNETIC IMAGES OF THE HEAD IN MAGNETIC STIMULATION OF THE BRAIN

The method disclosed below, by means of which some selected MR image set (standard head) of a head can be deformed, in such a way that its external shape corresponds to the shape of the surface of the head of another test subject or patient.

If it is wished to focus the magnetic stimulation on a specific area of the brain, magnetic-resonance images of the patient's head are often used. In that case, the location and orientation of the coil, which acts as the element evoking a responds in magnetic stimulation, relative to the patient's head, is determined using a suitable localizing system. After this, the location of the coil can be mapped in the magnetic-resonance images, so that the operator can easily focus the stimulation on the desired point. One such method is disclosed in patent application FIxxxxx.

Correspondingly, magnetic-resonance images are used in other cases too, when it is desired to locate some functional part of the brain relative to the cerebral anatomy. The brain function can be detected and located using, for instance, electroencephalographyic and magnetoencephalographyic means. In both methods, up to tens of measuring channels are typically used, which measure the electromagnetic fields associated with brain activity at different points on the head or scalp of the patient. If the locations of the measuring sensors relative to the head are known precisely, the brain functions can be localizeed and compared with the anatomical structure at the point in question that can be seen from the magnetic-resonance images.

One problem with the methods and equipment according to the prior art is that separate magnetic-resonance images are required of the heads of each patient or test subject. Magnetic-resonance images of the head are expensive, so that TMS, EEG, and MEG examinations are also expensive.

A second problem is that, if magnetic-resonance images of a patient's head are not available,

or if it is not wished to use them, it will be difficult to determine even roughly the point of the surface of the head, beneath which a specific area of the brain is located. This is because there are great variations in the shape and size of the heads of different people. In one typical TMS examination, it is wished to focus the stimulation on the prefrontal area of the left cerebral hemisphere by placing a figure-of-eight stimulation coil on top of the area in question. In one typical MEG examination, brain activity relating to a motor task is detected from two different points in the brain. One of the points can be interpreted with certainty, on the basis of, for instance, a waveform, as relating to activity of the somatosensory cortex, but it is not possible to determine the anatomic locus of the other without magnetic-resonance imaging.

A third problem is that

In known deforming methods, the magnetic-resonance images are deformed in such a way that they correspond, for example, to computer tomography images. In that case, several fixed points, which can be seen in both image series, are sought from both image series. It is possible to create deforming imaging, which brings both image series into the same set of co-ordinates.

Deforming methods are also known, which seek to correct MRI images in such a way that allowance is made for the non-ideal nature of magnetic-resonance imaging, such as the non-linearity of the gradient fields. In the methods, correction factors are measured or calculated and the images are deformed according to them.

Methods are also known, in which MRI images taken of different peoples are deformed by, for instance, stretching and shrinking, in such a way that the same anatomical or functional fixed are sought from the images of each person. After this, imaging is created separately for each person, which depicts the images of the person in such a way that the selected fixed points of the deformed image series coincide for all the test subjects. One such known method is the Talaraich method (Talaraich J., Tournoux P. Co-planar Stereotaxic Atlas of the Human Brain. New York, Thieme Medical Publishers Inc. 1988). The aim of the method is to

deform the MRI of the different subjects in such a way that it becomes possible to compare with each other the MRI images of the different subjects.

The invention is intended to create a new type of method, in which it is possible to determine the approximate located of the most important areas of a person's brain without focussing the magnetic stimulation of magnetic-resonance imaging.

The invention is based on that fact that, in the method, the shape of the head of a patient or test subject (1. person A) by localizing the points on the scalp using a localizing system. Preferably some tens of points, but at least five (forehead, left side, right side, occiput, crown of the head) are localized. Similarly, the shape of the head is correspondingly determined for a second person (person B) from magnetic-resonance images of the head. The images of person B are deformed by a computational system using translation, rotation, and linear and/or non-linear scaling, in such a way that they correlate to the shape of the scalp of the patient. The images of person B can also be referred to as a *standard head*.

During deformation, the shape of the external surface of the head sought from the MRI images of the standard head the location of the anatomical structures of the inside of the head are also altered in such a way that a linear or non-linear depiction is created.

As a second part of the invention, it is possible in addition to use functional fixed points. In that case, the location of the motor cortex can be determined from a patient by magnetic stimulation or electroencephalography or magnetoencephalography or infrared tomography. The same is done beforehand to another person (person B, standard head), of whose head there are existing magnetic-resonance images. Based on the magnetic-resonance images, the shape of the brain is modelled in such a way that the location of the motor cortices of the patient and the second person correlate. Similarly, it is possible to proceed by using several different functional fixed points, such as the motor cortex of one cerebral hemisphere or the visual cerebral cortex. It is also possible to use the location of a functional fixed point, which is predefined statistically for several people.

TMS is an example of the use of functional points in deformation. The location of the motor cortex can be determined easily by moving the coil on the top of the head until a strong muscular response (EMG) is detected from the muscles of the hand on the opposite side. This can be done to both cerebral hemispheres. In deformation, a suitable weighting factor is used to set the locations of the motor cortexes of persons A and B to be the same. After that

The localizing system can be based, for example, on the use of infrared light or electromagnetic fields. Such methods are available from, for example, the Canadian company Northern Digital Inc. The localizing system is first used to determine the location of even some selected fixed points on the head relative to each other. Suitable fixed points are, for example, the nasion, the inion, and the preauricular points located in front of the ears. In addition, a group of other points are located on the scalp. These points are preferably located on both sides of the head. The more points there are, the better the deformation will succeed.

Deformation can be performed, for instance, as follows. Standard head 1. Magnetic-resonance images of person B, the image area of which covers the entire head, are first segmented in such a way that the co-ordinates of the points on the surface of the head are determined from the images. Next, a localizing device is used to determine points on the surface of the scalp of person A, according to the method described above. Next, some suitable linear or non-linear deformation algorithms are used, such as those known from the publication XXX, which deform the magnetic-resonance images of person B, in such a way that the surface of the scalp defined from the deformed images corresponds to the shape of the head of person A. [a more detailed description here].

An essential part of the method is that the magnetic stimulation coil, the EEG electrodes, or MEG measuring sensors are localized relative to the head of the person by locating using a localizing system. Thus, a localizing sensor is attached to the head of the person, the location of which can be determined using the localizing system. The localizing system is then used to define at least three fixed points on the head (which can also be found in the MRI images) and co-ordinate-set conversion imaging is created.

Considerable advantages are gained with the aid of the invention.

[some facts about the head here]

One considerable advantage is that magnetic-resonance images of the patient need not be taken to evaluate the anatomy of the head for the focussing of magnetic stimulation.

A second advantage is that the stimulation results of different patients can be compared in a standard head.

One embodiment of the invention is ... to use the method as an atlas.

[a remaining problem is, among others, the use on patients, whose functions and anatomic structures have moved as a result of disease or trauma.]

CLAIMS:

1. Method in the deformation of magnetic-resonance images for focussing magnetic stimulation and visualizing the field of effect, in which method

- the magnetic-resonance images of some other person are deformed in such a way that the shape of the head of the person to be stimulated corresponds to the shape of the head defined from the deformed magnetic-resonance images of the other person.

characterized in that

- the shape of the external surface of the head is determined by using a localizing system to locate the co-ordinates of at least three points on the scalp

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2. ... the localizing system is based on the use of infrared light, electromagnetic fields, or laser light.

3. ... the deformation algorithm includes, in addition, a possibility for deformation in such a way that, in the deformed image pack, the distance between the surface of the brain and the scalp corresponds to the distance specific to persons of the age of the person in question.

4. ... in deformation, in addition to, or instead of surface points, the locations of such functional points in the brain are used, which can be determined without magnetic-resonance imaging, such as the location of a function measured by magnetic stimulation, MEG, or EEG.

5. ... in deformation, minimization algorithms are used, which minimize the distance between the points on the surface of the deformed head and the points measured on the surface of

another person.

... in minimization, it is accepted that the distances are not zero for all points.

... the method is used, when the TMS, EEG, or MEG responses are visualized in an illustrative manner for a patient, for whose head magnetic-resonance images are not available.

KOKOUS [redacted] klo 13.30

AIHE: Standardipää

Karhu ja Ruohonen esittelivät ajatuksen käyttää TMS/MEG/EEG tutkimuksissa MRI standardipäätä. Menetelmässä määritetään paikannuslaitteella henkilön pään ulkopinta ja deformoidaan toisen henkilön MRI kuvat siten, että ulkomuodot vastaavat toisiaan.

Menetelmästä on hyötyä TMS/MEG/EEG mittausten suunnittelussa, analysoinnissa ja visualisoinnissa. Erityisesti voidaan käyttää visualisointityökaluja myös silloin, kun jostain koehenkilöstä/potilaasta ei ole saatavilla MRI kuvia.

Läsnäolijat saivat luottamuksellisen [redacted] päivätyn patenttihakemusmuotoon kirjoitetun 8-sivuisen kuvauksen menetelmästä.

Antti Ahonen, 4D Neuroimaging

Jari Karhu, Nexstim

Jarmo Ruohonen, Nexstim

PATENTTIHAKEMUS

PÄÄN MAGNEETTIKUVIEN MUODON MUOKKAAMINEN AIVOJEN MAGNEETTISTIMULAATIOSSA SEKÄ ELEKTRO- JA MAGNETOENKEFALOGRAFIASSA

KEKSIJÄ
JARMO RUOHONEN

HAKIJA
NEXSTIM OY

PÄÄN MAGNEETTIKUVIEN MUODON MUOKKAAMINEN AIVOJEN MAGNEETTISTIMULAATIOSSA

Alla kuvataan menetelmä, jolla voidaan deformoida jotain valittua pään MR-kuvapakkaa (standardipää) siten, että se vastaa ulkomuodoltaan toisen koehenkilön tai potilaan pään pinnan muotoa.

Kun magneettistimulaatio halutaan kohdentaa tietylle aivojen alueelle, käytetään usein potilaan pään magneettikuvia. Tällöin magneettistimulaation heräte-elimenä toimivan kelan sijainti ja asento potilaan pään suhteen määritetään sopivalla paikannusjärjestelmällä. Tämän jälkeen kelan sijainti voidaan esittää magneettikuvissa, jolloin käyttäjä voi helposti kohdistaa stimulaation haluamaansa kohtaan. Eräs tällainen menetelmä kuvataan patenttihakemuksessa FIxxxxx.

Vastaavasti pään magneettikuvia käytetään muulloinkin, kun halutaan paikantaa jokin aivojen toiminnallinen osa aivojen anatomian suhteen. Aivotoimintaa voidaan havaita ja paikantaa mm. elektroenkefalografian ja magnetoenkefalografian keinoin. Molemmissa menetelmissä käytetään tyypillisesti jopa kymmeniä mittakanavia, jotka mittaavat aivojen toimintaan liittyviä sähkömagneettisia kenttiä eri kohdista pään päältä tai pinnalta. Kun mitta-anturien paikat tunnetaan tarkasti pään suhteen, voidaan aivojen toimintoja paikantaa ja verrata, mitä magneettikuvista nähtävää anatomista rakennetta kyseinen paikka vastaa.

Eräänä ongelmana tunnetun tekniikan mukaisilla menetelmillä ja laitteilla on, että jokaisen potilaan tai koehenkilön päästä tarvitaan magneettikuvat erikseen. Pään magneettikuvat ovat kalliita, jolloin myös TMS, EEG, MEG tutkimukset tulevat kalliiksi.

Toisena ongelmana on, että jos potilaan pään magneettikuvia ei ole käytettävissä tai niitä ei haluta

käyttää, on vaikeata osoittaa karkeastikaan pään pinnalta sitä kohtaa, jonka alla tietty aivojen alue sijaitsee. Tämä johtuu siitä, että pään muoto ja koko vaihtelevat ihmisillä suuresti. Eräässä tyypillisessä TMS kokeessa halutaan kohdistaa stimulaatio vasemman aivopuoliskon prefrontaaliselle alueelle asettamalla kahdeksikon muotoinen stimulaatiokela kyseisen alueen päälle. Eräässä tyypillisessä MEG kokeessa havaitaan motoriseen tehtävään liittyvää aivotoimintaa kahdesta eri aivojen kohdasta. Toinen kohta voidaan mm. käyrämuodon perusteella varmuudella tulkita liittyvän somatosensorisen korteksin toimintaan, mutta toisen komponentin anatomista vastinetta ei pystytä kertomaan ilman magneettikuvausta.

Kolmantena ongelmana on, että

Tunnetuissa deformoivissa menetelmissä magneettikuvia deformoidaan siten, että ne vastaavat esimerkiksi tietokonetomografiakuvia. Tällöin molemmista kuvasarjoista haetaan useita kiintopisteitä, jotka ovat näkyvissä molemmissa kuvasarjoissa. Voidaan muodostaa deformoiva kuvaus, joka saattaa molemmat kuvasarjat samaan koordinaatistoon.

Tunnetaan myös deformoivia menetelmiä, joissa MRI kuvia pyritään korjaamaan siten, että otetaan huomioon magneettikuvauksen epäideaalisuuksia kuten gradienttikenttien epälineaarisuus. Menetelmissä mitataan tai lasketaan korjauskertoimet ja deformoidaan kuvat niiden mukaisesti.

Tunnetaan myös menetelmiä, joissa eri henkilöiltä otetut MRI kuvat deformoidaan mm. venyttämällä ja kutistamalla siten, että jokaisen henkilön kuvista etsitään samat anatomiset tai toiminnalliset kiintopisteet. Sen jälkeen muodostetaan erikseen joka henkilölle kuvaus, joka kuvaa henkilön kuvat siten, että deformoidun kuvasarjan valitut kiintopisteet ovat yhtyvät kaikille koehenkilöille. Eräs tällainen tunnettu menetelmä on Talaraich-menetelmä (Talairach J, Tournoux P. Co-planar Stereotaxic Atlas of the Human Brain. New York, Thieme Medical Publishers, Inc.

1988). Menetelmän tavoitteena on deformoida eri henkilöiden MR kuvat siten, että voidaan vertailla eri henkilöiden aivojen MR kuvia keskenään.

Keksinnön kohteena on aikaansaada uudentyyppinen menetelmä, jossa voidaan määrittää henkilön aivojen tärkeimpien alueiden karkea sijainti ilman magneettikuvausta magneettistimulaation kohdentamista. Menetelmä on erityisen hyödyllinen magneettistimulaation kohdentamisessa; ja magneettistimulaation, EEG:n, MEG:n tulosten analysoinnissa ja visualisoinnissa.

Keksintö perustuu siihen, menetelmässä määritetään potilaan tai koehenkilön (1. henkilö A) pään muoto paikantamalla päänahalta pisteitä paikannusjärjestelmällä. Edullisesti pisteitä paikannetaan joitain kymmeniä, mutta ainakin viisi (otsa, vasemmalta, oikealta, takaraivosta, ja päälaelta). Samoin jonkun toisen henkilön (henkilö B) pään magneettikuvista määritetään vastaavasti pään muoto. Henkilön B kuvia deformoidaan laskentasysteemillä käyttäen translaatiota, rotaatiota ja lineaarista ja/tai epälineaarista skaalausta siten, että ne korreloivat potilaan päänahan muodon kanssa. Henkilön B kuvia voidaan myös kutsua ***standardipääksi***.

Deformoitaessa standardipään MRI kuvista haetun pään ulkopinnan muotoa myös pään sisäpuolen anatomisten rakenteiden sijaintia muutetaan siten, että muodostuu lineaarinen tai epälineaarinen kuvaus.

Toisena keksinnön osana voidaan lisäksi käyttää funktionaalisia kiintopisteitä. Tällöin määritetään esimerkiksi potilaalta hänen motorisen aivokuoren sijainti magneettistimulaatiolla tai elektroenkefalografialla tai magnetoenkefalografialla tai infrapunatomografialla. Sama tehdään etukäteen toiselle henkilölle (henkilö B, standardipää), josta on olemassa pään magneettikuvat. Magneettikuvista pääteltyä aivojen muotoa muokataan siten, että potilaan ja toisen henkilön motorisen aivokuoren sijainnit korreloivat. Samoin voidaan menetellä käyttämällä useita eri funktionaalisia kiintopisteitä

kuten toisen aivopuoliskon motorinen aivokuori tai visuaalinen aivokuori. Voidaan myös käyttää funktionaalisen kiintopisteen sijaintia, joka on määritetty etukäteen tilastollisesti usealle henkilölle.

Esimerkkinä toiminnallisten pisteiden käyttämisestä deformoinnissa on TMS. Liikeaivokuoren sijainti voidaan määrittää helposti siirtelemälle kelaa pään päällä kunnes havaitaan voimakkain lihasvaste (EMG) vastakkaisen puolen käden lihaksista. Tämä voidaan tehdä molemmille aivopuoliskoille. Deformoinnissa asetetaan sopivalla painokertoimella henkilön A ja B liikeaivokuorten sijainnit samoiksi. Sen jälkeen

Paikannusjärjestelmä voi perustua esimerkiksi infrapunavalon tai sähkömagneettisten kenttien käyttöön. Tällaisia menetelmiä on saatavilla esimerkiksi kanadalaiselta Northern Digital Inc. -yritykseltä. Paikannusjärjestelmällä määritetään ensin joidenkin valittujen pään kiintopisteiden sijainti suhteessa toisiinsa. Sopivia kiintopisteitä ovat esimerkiksi nenän syvennys (nasion), takaraivon kuhmu (inion) ja korvien edessä sijaitsevat preaurikulaariset pisteet. Lisäksi paikannetaan joukko muita pisteitä päänahalta. Edullisesti nämä pisteet sijaitsevat eri puolilla päätä. Mitä enemmän pisteitä on, sitä paremmin deformointi onnistuu.

Deformointi voidaan tehdä vaikkapa seuraavasti. Standardipää 1. henkilön B magneettikuvat, joiden kuva-alue kattaa koko pään, segmentoidaan aluksi siten, että kuvista määritetään pään pinnan pisteiden koordinaatit. Seuraavaksi määritetään henkilön A päänahan pinnan pisteitä edellä kuvatun menetelmän mukaisesti paikannuslaitteella. Seuraavaksi käytetään jotain soveltuvaa lineaarista tai epälineaarista deformointialgoritmia, kuten vaikkapa julkaisusta XXX tunnettua, joka deformoi henkilön B magneettikuvat siten, että deformoiduista kuvista määritetty päänahan pinta vastaa henkilön A pään muotoa. [tähän tarkempi kuvaus].

Menetelmään liittyy oleellisesti, että magneettistimulaation kelaa, EEG:n elektrodeja tai MEG:n mitta-antureita paikannetaan henkilön pään suhteen paikantamalla ne paikannusjärjestelmällä. Tällöin henkilön päähän kiinnitetään paikka-anturi, jonka paikka voidaan määrittää paikannusjärjestelmällä. Paikannusjärjestelmällä määritetään sitten ainakin kolme kiintopistettä päästä (jotka ovat myös löydettävissä MRI-kuvista) ja muodostetaan koordinaatistomuunnoskuvaus.

Keksinnön avulla saavutetaan huomattavia etuja.

[tähän päältä asioita]

Yhtenä huomattavana etuna on, että potilaasta ei tarvitse ottaa magneettikuvia pään anatomian arviointiin magneettistimulaation kohdentamista varten.

Toisena etuna on, että voidaan verrata eri potilaiden stimulaatiotuloksia standardipäässä.

Keksinnön yksi sovellusmuoto on ... käyttää menetelmää atlaksena.

[jäljelle jää ongelma mm. käytöstä potilailla, joilla toiminnot ja anatomiset rakenteet voivat olla siirtyneet sairauden tai trauman seurauksena.]

PATENTTIVAATIMUKSET:

1. Menetelmä aivojen magneettikuvien deformointiin magneettistimulaation kohdentamista ja vaikutuskentän visualisointia varten, jossa menetelmässä

- deformoidaan jonkun toisen henkilön magneettikuvat siten, että stimuloitavan henkilön pään muoto vastaa toisen henkilön deformoiduista magneettikuvista määritettyä pään muotoa.

tunnettu siitä, että

- pään ulkopinnan muoto määritetään paikantamalla paikannusjärjestelmällä ainakin kolmen pisteen koordinaatit päänahalta

-

-

2. ... paikannusjärjestelmä perustuu infrapunavalon, sähkömagneettisten kenttien tai laservalon käyttöön.

3. ... deformointialgoritmi sisältää lisäksi mahdollisuuden deformointiin siten, että deformoidussa kuvapakassa aivojen pinnan ja päänahan välinen etäisyys vastaa kyseisen henkilön ikäisille henkilöille ominaista etäisyyttä.

4. ... deformoinnissa käytetään pintapisteiden lisäksi tai niiden sijasta sellaisten aivojen toiminnallisten pisteiden sijaintia, jotka pystytään määrittämään ilman magneettikuvausta kuten magneettistimulaatiolla, MEG:llä tai EEG:llä mitattua toiminnon sijaintia aivoissa.

5. ... deformoinnissa käytetään minimointialgoritmiä, joka minimoi deformoidun pään pinnan pisteiden ja toisen henkilön mitattujen pään pinnan pisteiden välisen etäisyyden.

... minimoinnissa hyväksytään, että etäisyydet eivät ole nolla kaikille pisteille.

... menetelmää käytetään, kun visualisoidaan havainnollisella tavalla TMS, EEG tai MEG vasteita potilaalle, jonka pään magneettikuvia ei ole saatavilla.

CONFIRMATION

Being familiar with both the Finnish and the English languages, I herewith confirm that the attached document is a true translation of the basic Finnish Patent Application No. 20021858 filed with the Finnish Patent Office on October 17, 2002 in the names of Nexstim Oy and 4-D Neuroimaging Oy.

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Method for three-dimensional modeling of the skull and internal structures thereof

The invention relates to a method according to the preamble of claim 1 for three-dimensional modeling of the skull and internal structures thereof.

This patent application describes a method suited for modifying a set of magnetic resonance images taken from the head (standard head) so that the external shape of the head determined from such a set of images can be transformed to correlate with the contour of the head of another test person or patient. The present method is particularly suited to the magnetic stimulation of the brain as well as to electro-encephalography and magnetoencephalography.

In transcranial magnetic stimulation (TMS) of the brain, a coil excited with a strong current pulse of short duration is placed over the head. As a result, an electric current stimulating cerebral tissue is induced inside the skull. In order to focus the magnetic stimulation on a certain selected area of the brain, it is often necessary to resort to the magnetic resonance images taken from the test person's or patient's head. Herein, the location and orientation of the coil acting as the response-evoking means of magnetic stimulation is determined in regard to the coordinates of the patient's head with the help of a suitable localizing system. Subsequently, the location of the coil can be mapped on the magnetic resonance images (MRI) of the patient, whereupon the system operator can readily focus the stimulation on a desired area. One such method is described in FI Pat. Appl. 20021416.

Respectively, the magnetic resonance images of the patient's head are utilized when there is a need for locating a functional cerebral part in the anatomy of the brain. Brain functions can be recorded and located using conventional methods such as electro- and magnetoencephalography (EEG and MEG). Both of these methods typically use tens or even hundreds of measurement channels that sense electromagnetic fields evoked by brain activity at different points about the head or on the scalp. By knowing the exact locations of the measurement sensors relative to the head

coordinates, it becomes possible to identify brain functions and to visualize the anatomical structure of each point in the magnetic resonance images.

Conventionally, the head anatomy of the patient or test person being examined is first recorded by taking anatomical magnetic resonance images or other type of images resolving anatomical structures. Next, at least three fixed marker points are selected on the head surface such that they can readily be identified on both the magnetic resonance images and the surface of the head. Advantageously, the auditory meatuses and the nasion, for instance, are chosen to serve as marker points. As a result, a coordinate transformation can be formulated suitable for identification of a point in the magnetic resonance images corresponding to a certain point on the surface of the head. Thus, e.g., the location of a TMS coil in regard to anatomical structures can be ascertained or, alternatively, a stimulus-responsive point in the brain located with the help of MEG can be located in regard to anatomical structures. Various techniques are available for making a suitable coordinate transformation. Magnetic resonance images of the test person's head are required in the implementation of this method.

Using known methods, magnetic resonance images can be deformed so as to provide correlation with the respective computer-aided tomography images. The deformation method is called image fusion. In this process, both ones of the sets of images are analyzed to find a plurality of fixed marker points that are identifiable in both image sets. Subsequently, a deforming transformation can be carried out such that the corresponding points of the images to be matched become aligned with each other.

In the art are also known methods for warping magnetic resonance images taken by MRI techniques from a test person so that the nonideal properties of magnetic resonance imaging such as the nonlinearity of gradient fields, are corrected. In these methods, correction factors are measured or computed and thereupon the images are respectively deformed. In EP patent publication 1 176 558 is further described a method for external patient contouring with the help of a suitable surface imaging

system, whereupon the information thus gathered is used to deform the patient's MRI images for planning a radiotherapy treatment.

Further methods known in the art are based on deforming by dilatation and contraction warping techniques a set of MRI images taken from different persons so that first the same fixed anatomical or functional marker points are identified in the images of each one of test persons individually. Thereupon a mathematical mapping is computed individually for each test person such that the test person's MRI images are transformed in a fashion allowing the selected marker points of the deformed image sets to have the same coordinates for all the test persons. One such method is the so-called Talairach cerebral imaging system (J. Talairach and P. Tournoux, Coplanar Stereotaxic Atlas of the Human Brain, New York, Thieme Medical Publishers, Inc., 1988). The goal of this system is to deform the MRI images of different persons so that the MRI images of the different persons' brains can be compared with each other.

The above-described methods have in common that all of them need anatomical images of the test person's head.

Still further in the art are known methods in which the head contour is determined by means of an imaging system and the thus mapped surface of the head is formed into a triangulated grid that serves as a mathematical model in the computation of electromagnetic fields associated with the use of MEG, TMS or EEG. Attempts have also been made to determine by statistical methods from the head contour such a triangulated grid that further represents the brain contour of the same test person. In this kind of method, magnetic resonance images are utilized to generate a statistical model representing correlation between the surfaces of the head contour and the brain contour. One such method is disclosed in publication D. van't Ent, J. C. de Munck, and Amanda L. Kaas, A Fast Method to Derive Realistic BEM Models for E/MEG Source Reconstruction, IEEE Trans. Biomed. Eng. (2001), BME 48(12):1434-1443. This method, however, is not used for processing MR images.

A problem hampering the use of the prior-art methods and apparatuses is that the analysis or visualization of data represented by the MRI images is possible only by taking the magnetic resonance images separately from each patient's or test person's head. Due to the high cost of magnetic resonance images of the head, also the overall cost of TMS, EEG and MEG examinations become high. Resultingly, the availability of TMS, MEG and EEG is limited.

If magnetic resonance images taken from the head of the person being examined are not available or the use thereof is not desirable, it is difficult to visualize even coarsely the area of the skull hiding a given brain region of interest. The basic reason hereto is that the head contour and size vary largely from person to person.

In a typical TMS examination, for instance, it may be desirable to focus the magnetic stimulus on the prefrontal region of the left hemisphere by placing a figure-of-eight stimulation coil at the desired area of the head. However, it is difficult to select the proper area on the head if no anatomical images of the interior structures of the head are available. Respectively in a typical MEG and EEG recording session a response is discovered relating to a certain task, which can be located inside the head in relation to marker points situated external to the head. Lacking access to anatomical images illustrating the interior structures of the head, however, it is difficult to tell the anatomical part of the brain that coincides with the identified point of response.

In another typical MEG or EEG examination, the task may be to identify brain activity at two different regions of the brain as a response to, e.g., a task involving motor skills. In this exemplary case, the first region can be positively identified based on such variables, among others, as the characteristic waveform of the response to represent the function of the motor cortex, while the anatomical locus of the other component of the response cannot be located without resorting to magnetic resonance imaging or other techniques such as computer-aided tomography suited for resolving anatomical structures.

It is an object of the present invention to provide an entirely novel kind of method capable of overcoming the problems of the above-described prior art.

Accordingly, the invention strives to achieve a fully new approach to the approximate localization of the major brain regions in a test person's head without the need for magnetic resonance imaging. The method is particularly useful in the focusing of magnetic stimulation and in the interpretation and visualization of results obtained by means of magnetic stimulation, EEG and MEG. This facility can be employed, e.g., for making screening measurements for large groups of patients without the need for taking costly MRI images from each patient individually.

The goal of the invention is attained by virtue of modeling the coordinates of the test person's head as to its different internal anatomical regions and particularly its different brain regions on the basis of the test person's head contour and, additionally, on the basis of the different internal anatomical regions, particularly its different brain regions, actually recorded from the head of another test person.

More specifically, the method according to the invention is characterized by what is stated in the characterizing part of claim 1.

The invention offers significant benefits.

One major advantage is that the patient need not be subjected to magnetic resonance imaging to identify the internal anatomy of the patient's head for proper focusing of magnetic stimulation or analysis of MEG and EEG recordings.

Another advantage is that the method allows the stimulation responses of different patients to be compared with each other in the coordinate system of a "standard head".

A third advantage is that a deforming image transform can be carried out or refined using functional marker points identified in the interior volume of the brain.

A still further advantage is that the method makes it possible to readily indicate without anatomical imaging the coarse coordinates of a point on the head surface under which a given anatomical brain region is located. Furthermore a coarse location of a given brain anatomical region under a selected point on the head surface is possible without the need for magnetic resonance imaging.

In the following the invention will be examined with the help of exemplary embodiments and by making reference to the appended drawing in which

FIG. 1 is a schematic illustration showing the use of a method according to the invention in a single plane.

Referring to FIG. 1, the upper diagram shows a single plane of accurate magnetic resonance images taken from the head of a test person B. Test person A is measured only for the external dimensions of the head in order to draw the sectional plane A shown in the middle diagram. According to the invention, the coordinate data of diagram B are dilated and/or contracted (that is, scaled) so as to fit the data within the confines of sectional plane A, whereby the diagram of sectional plane A is transformed into a modeled sectional diagram A'. In the exemplary case, it has been necessary to dilate the diagram shape of sectional plane B in the vertical direction and to contract in the horizontal direction.

The above-described procedure is applied entirely identically also in the height direction, whereby three-dimensional modeling is attained.

Accordingly, the invention is based on using a method wherein the head contour of the person (first person A) being examined is determined by measuring the coordinates of selected marker points on the scalp with the help of a localization system. Advantageously, the number of measured marker points is some tens and they are located at different sides of the head. The greater the number of measured marker points the better is the result of the deformation process. Already five marker points

on the head (forehead, left side, right side occipital protuberance and parietal top) give relatively accurate results. Next, the head contour of some other person (person B) is determined from magnetic resonance images taken earlier from this person's head. The images of person B are deformed (scaled) computationally using translation, rotation and linear and/or nonlinear deformation so as to make the shape of the head images correlate with the contour of the person's scalp, whereby a deforming linear or nonlinear transformation between both shapes takes place. The head images taken from person B may also be called a standard head. In the method the transformation is applied volumetrically to the entire sets of magnetic resonance images, that is, also to coordinates located in the interior volume of the head. Herein the location and shape of the anatomical structures may become distorted. It is also possible to use a plurality of standard heads (e.g., separately for adults and children), whereby a standard head of closest fit can be individually selected for each patient. Also the racial differences between head contours can be taken into account by maintaining a selection of different standard heads. Advantageously, the standard head is computed using a set of MRI images having a good resolution, e.g., 256×256 pixels in each sectional plane.

Image deformation (scaling) can be carried out, for instance, in the following manner. First, the magnetic resonance images of the standard head, that is, those taken from the head of person B, covering an entire sectional plane of the head are segmented by determining the coordinates of selected marker points on the skull surface. Next, selected points of the scalp of person A being examined are determined in the earlier described fashion using a localizing system. Thereupon a suitable linear or nonlinear deformation algorithm is carried out such that the magnetic resonance images of person B are deformed maximally well to correlate with the head shape of person A. The deformation transform may also be incomplete, whereby the shapes of the two heads are not aggressively deformed to full correlation. Suitable deformation algorithms are extensively described in the literature of the art. The magnetic resonance images can be represented digitally in any known graphic format such as pixel or vector graphics.

One exemplary deformation technique comprises determining from the magnetic resonance images of person B the location of, e.g., five marker points (the left and right auditory meatuses, the nasal bend also called the nasion, the occipital protuberance also called the inion and the parietal top). The respective marker points are determined with the help of localizing system from the head surface of the person being examined. First, the marker points are registered with each other by way of carrying out a transformation that by translation and rotation makes the respective marker points of the heads of persons A and B to converge with each other. Subsequently, a linear scaling algorithm can be applied to the magnetic resonance images of test person B can be subjected to linear scaling such that the respective marker points unite with each other. As a result, a deforming transform takes place capable of making the head shape identified from the magnetic resonance images of person B to correlate coarsely with the head shape of person A. When necessary, the procedure may be similarly extended to correlation of a larger number of marker points.

One possible deformation procedure comprises the use of an algorithm described in publication J. Lötjönen, et al.: Model Extraction from Magnetic Resonance Volume Data Using the Deformable Pyramid, Medical Image Analysis, Vol. 3, No. 4, pp. 387-406, 1999). First, the magnetic resonance images of person B are processed to determine marker points on the head surface, e.g., by image thresholding. The head contour of person A is determined at N points using a localizing system. Both sets of points are registered with each other by way of performing translation and rotation operations such that make the sets of points to converge with each other maximally well. When using optimally selected translation and rotation operators, one possible strategy is, for instance, to aim at a minimum sum of squares of differences between local radii of curvature on the correlating surfaces. Next, the magnetic resonance images are divided into a cubic grid of 3×3×3 voxels. An energy function E is defined that may be, e.g., the sum of distances from the points of image set A to the respective next closest point of image set B. Also for each elementary cube of the grid is written a deformation function f(x,y,z) that typically is a spline or polynomial function (such as Bernstein polynomials) and thus defines the amount of translation

at other points of the cubic grid caused by a shift of one corner point of the grid. Generally, the amount of grid deformation becomes the smaller the larger the distance of the grid point from the corner point. The deformation function may be linear or nonlinear. Next, the locations of the grid points are translated so as to minimize energy function E. As a result, the elementary cubes of the initially perfect cubic grid are dilated or contracted and thus deformed. The deformation function f is applied to each elementary cube. After the minimization of energy function E, the surfaces of the heads correlate with each other. In practice, also certain boundary conditions must be defined for the cubic grid. For instance, it may be advantageous to confine the dilation of the individual elementary cubes so that the dilation of all elementary cubes is uniform. Such a suitable boundary condition may be implemented in energy function E.

In another embodiment of the invention, also functional marker points of the brain may be utilized. Herein, the localization of the motor cortex area of a person being examined but not having MR images of the head available can be carried out by magnetic stimulation or, alternatively, using electroencephalography or magnetoencephalography or infrared tomography. Localization is performed relative to external marker points of the head (e.g., ears and nose). Similar localization is performed in beforehand for another person (person B serving as a standard head) for whom the magnetic resonance images of the head are available. The localization of the motor cortex of person B is performed from the MR images. The set of magnetic resonance images is warped so as to make the locations of the motor cortex of the patient and the second person to correlate. Additionally, the MR images of person B are deformed so as to bring them into at least partial correlation with the head shape of the person being examined. A similar procedure is also applicable to the utilization of multiple different functional marker points such as the motor or visual cortical areas of both hemispheres. When so desired, it is also possible to utilize herein the location of such a functional marker point that has been determined by statistical methods for a plurality of persons.

An example of the use of functional marker points in image deformation is represented by TMS. With the help of this method, the location of the motor cortex can be readily determined by moving the stimulation coil over the head until the strongest muscle response (recorded by EMG) is detected in the hand muscles of the opposite side of the body. The same localization may be carried out for both hemispheres. Using suitable weights in the deformation procedure, the motor cortex locations of the person being examined and person B are made to coincide with each other.

An essential feature of the present method is that the locations of the magnetic stimulation coil, the EEG electrodes or the MEG sensors are measured relative to the test person's head coordinates using a localization system. Herein, on the person's head is mounted a position sensor whose location can be determined with the help of a localization system. The localization system is used for determining at least three marker points of the head (such that may also be identified in the MRI images), whereupon the deformation of the image coordinates can be performed. The localization system used in the invention can be based, e.g., on infrared radiation or electromagnetic fields. This kind of equipment is commercially marketed, e.g., by a Canadian company Northern Digital Inc., for instance.

In the context of the present application, scaling refers to a data processing method in which data generally representing an image is transformed into another form by linear or nonlinear procedures of dilatation/contraction warping of the image. An alternative term for this operation is deformation.

What is claimed is:

1. A method for modeling different internal structures of a head, such as different parts of the brain, in order to focus magnetic stimulation and/or visualize the results of magnetic stimulation, MEG or EEG, the method comprising the step of

- determining the location of the internal structures, such as the different cerebral parts, of at least one first head (B) in a three-dimensional space by technical means, e.g., magnetic resonance imaging or computer-aided tomography,

characterized in that

- the external dimensions of at least one second head (A) are determined, and
- the location data of said internal structures of said first head (B) are scaled in a three-dimensional space to correlate with said external dimensions of said second head (A), whereby the location data of the internal structures of said second head (A) also become modeled without the need for anatomical images of said second head (A).

2. The method of claim 1, **characterized** in that the method is utilized in the focusing of magnetic stimulation and/or visualization of results obtained by magnetic stimulation, MEG or EEG.

3. The method of any one of foregoing claims, **characterized** in that said location data is displayed in an image format and the scaling thereof is implemented by mutual moving of individual pixels.

4. The method of any one of foregoing claims, **characterized** in that the response recorded by MEG or EEG or, alternatively, the effective stimulating field of TMS is localized in relation to anatomical marker points determined on the head surface.

5. The method of any one of foregoing claims, **characterized** in that the measurement system of the external head dimensions is based on the use of infrared light,

electromagnetic fields, laser light or a pointer equipped with electrical position sensor means.

4. The method of any one of foregoing claims, **characterized** in that the image scaling algorithm includes an optional scaling facility that in the scaled set of superposed images adjusts the distance from the cortex to the scalp to a value typical for the person being examined in a cohort of persons of the same age.

6. The method of any one of foregoing claims, **characterized** in that, in addition to head surface marker points or in lieu thereof, the deformation operation is carried out utilizing the location data of such functional points of the brain that, without using magnetic resonance imaging, can instead be localized with the help of magnetic stimulation, MEG or EEG as functional points of the brain.

7. The method of any one of foregoing claims, **characterized** in that the image deformation is performed using a minimizing algorithm that minimizes the mutual distances between the respective points of the deformed image of head (A) and the points measured on the surface of a second person's head (B).

8. The method of any one of foregoing claims, **characterized** in that the computation results of the minimization algorithm are accepted even when the mutual distances between respective image points are not reduced to zero.

9. The method of any one of foregoing claims, **characterized** in that the method is utilized for visualizing in a layman fashion the results of TMS, EEG or MEG examinations performed on a patient having no magnetic resonance images of his/her head available.

10. The method of any one of foregoing claims, **characterized** in that the method is utilized in the display of results in a single set of MR images obtained from measurements performed on a plurality of test persons.

11. The method of any one of foregoing claims, **characterized** in that the standard head used in the method is selected from a library of plural magnetic resonance images taken from a plurality of persons representing heads of different types and shapes.

12. The method of any one of foregoing claims, **characterized** in that linear scaling is used in the method.

13. The method of any one of foregoing claims, **characterized** in that nonlinear scaling is used in the method.

[57] Abstract

A method is disclosed in this publication for modeling different internal structures of a head, such as different parts of the brain, the method comprising the step of determining the location of the internal structures, such as the different cerebral parts, of at least one first head (B) in a three-dimensional space by technical means, e.g., magnetic resonance imaging or computer-aided tomography. According to the invention, the external dimensions of at least one second head (A) are determined, and the location data of the internal structures of the first head (B) are scaled in a three-dimensional space to correlate with the external dimensions of the second head (A), whereby the location data of the internal structures of the second head (A) also become modeled without the need for anatomical images of the second head (A).

(Fig. 1)